Remarks

Upon entry of the above amendment, claims 1 to 12, 85 to 97, 100, 101, 115 to 129, and 135 to 150, are pending in the application, with claims 1, 85, 101, 115 and 138 being the independent claims. Claims 13 to 84, 98, 99, 102 to 114, and 130 to 134 are sought to be cancelled without prejudice or disclaimer of the subject matter therein. Amendment to claims 1, 2, 6, 7, 9, 10, 85, 86, 87, 90, 91, 96, 97, 100, 101, 115, 116, 123, 126, and 135 is sought. New claims 136 to 150 are sought to be added.

Amended claims 1, 2, 6, 7, 9, 10, 85, 86, 87, 90, 91, 96, 97, 100, 101, 115, 116, 123, 126, and 135 correspond to claims 1, 2, 6, 7, 9, 10, 85, 86, 87, 90, 91, 96, 97, 100, 101, 115, 116, 123, 126, and 135 of the parent application, 09/984,664, filed October 30, 2001, and correspond to Restriction Group I identified in the Office Action of March 13, 2003. Applicant has amended the claims to correct minor typographical or grammatical errors, and to make the language of the claims consistent throughout the present application. The subject matter of the amended claims is the same as the original claims, and introduce no new matter. Consideration and entry of the amended claims is respectfully requested.

New claims 136 to 150 are supported by the specification at *inter alia,* pages 5 to 14, 16, 18, 20 to 28, 35, 37, 41, 44, 47, 48, 50 to 55, 58 to 65, 68, 71, 73 to 79, 82 to 100, and the originally filed claims.

These new claims are believed to introduce no new matter, and their entry is respectfully requested.

Amendment to the Drawings

The deletion of Figures 29A, 29B and 29C is sought.

Changes are sought to correct obvious defects in the informal drawings, prior to submission of the formal drawings. Attached herewith is a "Request to Approve Proposed Drawing Corrections," copies of 4 sheet(s) of drawings, containing proposed corrections to Figures 3, 13, 14, and 15 shown in red. For comparison purposes, unmarked original and amended drawings are also provided. The proposed changes add no new matter to this application.

In Figure 3, the letter H had been overlaid on O, C, and N, obscuring the identity of the functional group. It is obvious to one of ordinary skill in the art that the correct functional groups are OH, CH_2, and NH or NH_2 respectively. Similarly, the negative charge sign (-) was incorrectly overlain upon certain O groups. The (-) has been moved so that the "O-" can be clearly seen.

In Figure 13, the 11^{th} letter in the second methylated strand should obviously be a letter G, not an A, corresponding to the letter G at the same position in the other 3 strands shown. Essentially the same nucleotide sequence is found in Figures 13 through 15.

In Figure 14, obvious errors in the sequence have been corrected to ensure that the sequences are the same in Figures 13, 14 and 15. To that end, the 11^{th} letter in both strands is changed from A to G; the 22^{nd} letter in the deaminated unmethylated DNA has been changed from G to A; and the fifth letter in the deaminated methylated DNA has been changed from Me-U to Me-C.

In Figure 15 it is clear that the nucleotide in the left and right strands do not correctly align. The DNA sequence in the left strand has now been shifted down one nucleotide, so that all nucleotides correctly align.

All of the above errors were most likely introduced as a result of an error by the original draftsman of the informal drawings and have been corrected in the replacement sheets of drawings. These corrections are sought to bring the drawings into conformity with the description.

Figures 29A, 29B and 29C have been cancelled. This cancellation has no effect on the patentability of the claims and thus are not required for written description or enablement support. To correctly number the subsequent Figures, renumbering of Figures 30 and 31 is sought. These changes introduce no new matter.

Applicant requests that the Examiner approve the proposed corrections. After official communication of such approval, Applicants will submit appropriately corrected formal drawings

Amendment to the Specification

In order for the specification to conform with the drawings following the deletion of Figures 29A, 29B and 29C, Applicant seeks amendment of the specification at paragraphs [0069] through [0071], and at [0244]. These amendments remove reference to the cancelled Figures, and renumber the subsequent Figures.

Amendment to the specification at the "CROSS REFERENCE TO RELATED APPLICATIONS" is sought to claim priority to a prior application.

Conclusion

Prompt and favorable consideration of this Preliminary Amendment is respectfully requested. Applicant believes the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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Version with markings to show changes made

In the Drawings

Figures 29A, 29B and 29C are deleted.

Figures 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 30 and 31; are substituted with the attached Figures 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 and 30.

In the Specification

The CROSS REFERENCE TO RELATED APPLICATIONS is new.

Paragraph [0069] is deleted.

Paragraphs [0070] and [0071] are amended as follows:

[0070] [FIG. 30.] FIG. 29. Portion of the contig sequence of the CDKN2A gene. The sequence represents a small portion of the contig starting at 856630 nucleotides from the start of the contig sequence. The sequence represents a CpG island. Contig number: NT_008410.4.

[0071] [FIG. 31.] FIG. 30. Schematic representation of a "capture probe" to determine the methylation status of a specific gene. Oligonucleotide probes that are specific for a region near the CpG island of the target gene are immobilized onto a microtiter plate. The DNA of interest is added to the immobilized probe and bound to the capture probe. The DNA is then chemically modified to convert unmethylated C to T, and leave methyl-C unaffected. The converted DNA can then be amplified by an optional PCR step to further enhance the signal. A labeled CpG initiator is then added with an RNA polymerase and labeled nucleotide(s).

Paragraph [0244] is amended as follows:

[0244] [As shown in Figure 29A, as] As the oligonucleotide product is generated, energy transfer occurs between TAMARA-SpApG and SF-UTP, which changes the wavelength at which TAMARA emits. If RNA polymerase or DNA is omitted from the reaction, there is no transfer of energy between the initiator and the terminator, and no change in the wavelength at which TAMARA emits [(Figure 29B and 29C)].

In the Claims

Claims 13 to 84, 98, 99, 102 to 114, and 130 to 134 are cancelled. Claims 136 to 150 are new.

The following claims 1, 2, 6, 7, 9, 10, 85, 86, 87, 90, 91, 96, 97, 100, 101, 115, 116, 123, 126, and 135 are amended as follows:

1. A method for detecting multiple reiterated oligonucleotides from a target DNA or RNA polynucleotide, said method comprising:

(a) hybridizing an initiator with a single stranded-target polynucleotide

(b) incubating said target polynucleotide and initiator with an RNA[-]polymerase, and a terminator;

(c) synthesizing multiple oligonucleotides from said target polynucleotide, wherein said initiator is extended until said terminator is incorporated into said oligonucleotide[s] thereby synthesizing multiple reiterative oligonucleotides; and

(d) detecting or quantifying said [reiteratively synthesized] reiterative oligonucleotide transcripts [of a polynucleotide of interest].

2. The method of claim 1, further comprising detecting or quantifying said [reiteratively synthesized] reiterative oligonucleotide transcripts by modifying a nucleoside or nucleotide in at least one of the members selected from the group consisting of said terminator, [and]

said initiator.

6. The method of claim 1, wherein said polymerase is selected from the group consisting of: a DNA-dependent RNA polymerase, an RNA-dependent RNA polymerase, [and] a modified RNA[-]polymerase, and a primase.

7. The method of claim 6, wherein said polymerase comprises an RNA polymerase derived from one of [E. coli, E. coli] *E. coli, E. coli* bacteriophage T7, [E. coli] *E. coli* bacteriophage T3, and [S. typhimurium] *S. typhimurium* bacteriophage SP6.

9. The method of claim 1, wherein said initiator comprises a molecule selected from the group consisting of: nucleosides, nucleoside analogs, nucleotide analogs and nucleotides of lengths from 1-25 nucleotides, 26-50 nucleotides, 51-75 nucleotides, 76-100 nucleotides, 101-125 nucleotides, and 126-150 nucleotides, 151-175 nucleotides, 176-200 nucleotides, 201-225 nucleotides, 226-250 nucleotides, and greater than 250 nucleotides[, and nucleotide analogs].

10. The method of claim 1, wherein said [abortive oligonucleotides] reiterative oligonucleotide transcripts being synthesized are one of the lengths selected from the group consisting of: about 2 to about 26 nucleotides, about 26 to about 50 nucleotides, [and] about 50 nucleotides to about 100 nucleotides, and greater than 100 nucleotides.

85. A method for detecting an oligonucleotide synthesized from a target [DNA] sequence, the method comprising:

(a) hybridizing a [DNA] primer with a single-stranded target [DNA] sequence;

(b) extending said [DNA] primer with a [DNA] polymerase and nucleotides, such that said [DNA] polymerase reiteratively synthesizes a nucleotide sequence; and

(c) detecting oligonucleotide comprised of repeat sequences synthesized by said [DNA] polymerase.

86. The method of claim 85, further comprising modifying at least one of said [DNA] primer and said nucleotides to enable detection of said oligonucleotide comprised of repeat sequences.

87. The method of claim 86, wherein modifying further comprises incorporating an independently selected label moiety into at least one of said [DNA] primer and said nucleotides.

90. The method of claim 85, wherein said [DNA] polymerase is selected from the group consisting of [Escherichia coli] *Escherichia coli* DNA polymerase, T7 DNA polymerase, T4 DNA polymerase, [Taq] *Taq* thermostable DNA polymerase, terminal transferase, and telomerase.

91. The method of claim 85, wherein said [DNA] primer comprises from 1 to about 25 nucleotides.

96. The method of claim 85, further comprising immobilizing said single-stranded target [DNA] sequence.

97. The method of claim 85, wherein immobilizing comprises hybridizing a capture probe to a portion of said single-stranded target [DNA] sequence.

100. The method of any one of claims 4, [17, 31, 45, 75,] 88, or 95 wherein said fluorophore moiety is selected from the group consisting of: 4-acetamido-4'-isothiocyanatostilbene-2,2'disulfonic acid; acridine and derivatives: acridine, acridine isothiocyanate; 5-(2'-aminoethyl)amninonaphthalene-1-sulfonic acid (EDANS); 4-amino-N-[3-vinylsulfonyl)phenyl]naphthalimide-3,5 disulfonate; N-(4-amino-1-naphthyl)maleimide; anthranilamide; BODIPY; Brilliant Yellow; coumarin, and derivatives: coumarin, 7-amino-

4-methylcoumarin (AMC, Coumarin 120), 7-amino-4-trifluoromethylcouluarin (Coumaran 151); cyanine dyes; cyanosine; 4',6-diaminidino-2-phenylindole (DAPI); 5', 5"-dibromopyrogallol-sulfonaphthalein (Bromopyrogallol Red); 7-diethylamino-3-(4'-isothiocyanatophenyl)-4-methylcoumarin; diethylenetriamine pentaacetate; 4,4'-diisothiocyanatodihydro-stilbene-2,2'-disulfonic acid; 4,4'-diisothiocyanatostilbene-2,2'-disulfonic acid; 5-[dimethylamino]naphthalene-1-sulfonyl chloride (DNS, dansylchloride); 4-dimethylaminophenylazophenyl-4'-isothiocyanate (DABITC); eosin and derivatives: eosin, eosin isothiocyanate; erythrosin and derivatives: erythrosin B, erythrosin, isothiocyanate; ethidium; fluorescein and derivatives: 5-carboxyfluorescein (FAM),5-(4,6-dichlorotriazin-2-yl)aminofluorescein (DTAF), 2',7'-dimethoxy-4'5'-dichloro-6-carboxyfluorescein (JOE), fluorescein, fluorescein isothiocyanate, QFITC, (XRITC); fluorescamine; IR144; IR1446; Malachite Green isothiocyanate; 4-methylumbelliferoneortho cresolphthalein; nitrotyrosine; pararosaniline; Phenol Red; B-phycoerythrin; o-phthaldialdehyde; pyrene and derivatives: pyrene, pyrene butyrate, succinimidyl 1pyrene; butyrate quantum dots; Reactive Red 4; rhodamine and derivatives: 6-carboxy-X-rhodamine (ROX), 6-carboxyrhodamine (R6G), lissamine rhodamine B, sulfonyl chloride rhodamine (Rhod), rhodamine B, rhodamine 123, rhodamine X isothiocyanate, sulforhodamine B, sulforhodamine 101, sulfonyl chloride derivative of sulforhodamine 101 (Texas Red); N,N,N',N'-tetramethyl-6-carboxyrhodamine (TAMRA); tetramethyl rhodamine; tetramethyl rhodamine isothiocyanate (TRITC); riboflavin; rosolic acid; terbiun chelate derivatives; Cy 3; Cy 5; Cy 5.5; Cy 7; IRD 700; IRD 800; La Jolla Blue; phthalo cyanine; and naphthalo cyanine.

101. A method for detecting multiple reiterated oligonucleotides from a target DNA or RNA polynucleotide, said method comprising:

(a) incubating a single-stranded target polynucleotide in a mixture comprising an initiator, and an RNA-polymerase;

(b) synthesizing multiple oligonucleotide transcripts from said target polynucleotide, wherein said initiator is extended until terminated due to nucleotide

deprivation, thereby synthesizing multiple abortive reiterative oligonucleotide transcripts; and

(c) detecting or quantifying said [reiteratively synthesized oligonucleotides] reiterative oligonucleotide transcripts.

115. A method for synthesizing multiple [reiterated oligonucleotides] reiterative olignucleotide transcripts from a target DNA or RNA polynucleotide, said method comprising:

(a) hybridizing an initiator with a single stranded target polynucleotide

(b) incubating said target polynucleotide and initiator with an RNA-polymerase, and a terminator;

(c) synthesizing multiple oligonucleotides from said target polynucleotide, wherein said initiator is extended until said terminator is incorporated into said oligonucleotides thereby synthesizing multiple reiterative oligonucleotide[s] transcripts.

116. The method of claim 115, further comprising synthesizing multiple reiterative oligonucleotide transcripts [oligonucleotides] by modifying a nucleotide in at least one of the members selected from the group consisting of said terminator, and said initiator.

123. The method of claim 115, wherein said reiterative oligonucleotide transcripts [abortive oligonucleotides] being synthesized are one of the lengths selected from the group consisting of: about 2 to about 26 nucleotides, about 26 to about 50 nucleotides and about 50 nucleotides to about 100 nucleotides.

126. The method of any one of claims 1, [13, 26, 27, 41, 54, 55, 56, 71, 72,] 101, [102, 103, 106, 112, 113, or] and 115, wherein said incubating further comprises in the presence of ribonucleotides.

135. The method of any one of claims 1, [13, 26, 27, 41, 54-56, 71, 72,] 85, 101[-103,

106, 112, 113, or] and 115, wherein said initiator is selected from the group consisting of: nucleosides, nucleoside analogs, nucleotides, [an] and nucleotide analogs.